Docket No. 245437US0/ims

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Fumiyuki SHIRAI, et al. GAU: 1614

SERIAL NO: 10/706,999 EXAMINER:

FILED: November 14, 2003

FOR: PYRAZOLE DERIVATIVES

REQUEST FOR PRIORITY

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

☐ Full benefit of the filing date of U.S. Application Serial Number , filed , is claimed pursuant to the provisions of **35 U.S.C. §120**.

☐ Full benefit of the filing date(s) of U.S. Provisional Application(s) is claimed pursuant to the provisions of **35 U.S.C. §119(e)**: **Application No.** **Date Filed**

■ Applicants claim any right to priority from any earlier filed applications to which they may be entitled pursuant to the provisions of **35 U.S.C. §119**, as noted below.

In the matter of the above-identified application for patent, notice is hereby given that the applicants claim as priority:

COUNTRY	APPLICATION NUMBER	MONTH/DAY/YEAR
AUSTRALIA	2002953019	December 2, 2002
AUSTRALIA	2002953602	December 30, 2002
AUSTRALIA	2003902015	April 29, 2003

Certified copies of the corresponding Convention Application(s)

■ are submitted herewith

☐ will be submitted prior to payment of the Final Fee

☐ were filed in prior application Serial No. filed

☐ were submitted to the International Bureau in PCT Application Number
Receipt of the certified copies by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

☐ (A) Application Serial No.(s) were filed in prior application Serial No. filed ; and

☐ (B) Application Serial No.(s)

☐ are submitted herewith

☐ will be submitted prior to payment of the Final Fee

Respectfully Submitted,

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Canberra

I, JANENE PEISKER, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002953019 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 02 December 2002.

WITNESS my hand this
Fourteenth day of November 2003

JANENE PEISKER
TEAM LEADER EXAMINATION
SUPPORT AND SALES

Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

A U S T R A L I A

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Azole Derivatives"

The invention is described in the following statement:

D E S C R I P T I O N

Azole derivatives

Technical Field

This invention relates to azole compounds having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

Background Art

The presence of two cyclooxygenase isoenzymes, cyclooxygenase-I (COX-I) and cyclooxygenase-II(COX-II)is known (Proc. Nat. Acad. Sci. USA 88, 2692-2696 (1991)).

Traditional non steroidal anti-inflammatory compounds (NSAIDs) have inhibiting activities of both COX-I and COX-II (J. Biol. Chem., 268, 6610-6614 (1993), etc). The therapeutic use thereof involves undesired effects on the gastrointestinal tract, such as bleeding , erosions, gastric and intestinal ulcers, etc.

It was reported that selective inhibition of COX-II shows anti-inflammatory and analgesic activities comparable with conventional NSAIDs but with a lower incidence of some gastrointestinal undesired effects (Pro. Nat. Acad. Sci. USA, 91, 3228-3232(1994)). Accordingly, various selective COX-II inhibitors have been prepared. However, it was reported that those "selective COX-II inhibitor" show some side-effects on kidney and/or insufficient efficacy on acute pains.

Further, some compounds such as SC-560, mofezolac, etc, which have certain selective inhibiting activity against COX-I. WO98/57910 shows some compounds having such activity. However, their selectivity of inhibiting COX -I does not seem to be enough to use them as a clinically acceptable and satisfactory analgesic agent due to their gastrointestinal disorders.

WO02/055502 shows some pyridine derivatives having cyclooxygenase inhibiting activity, particularly cyclooxygenase-I inhibiting activity. And WO99/51580 shows some

triazole derivatives having an inhibiting activity of cytokine production.

Disclosure of Invention

This invention relates to azole compounds, which have pharmaceutical activity such as cyclooxygenase (hereinafter described as COX) inhibiting activity, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

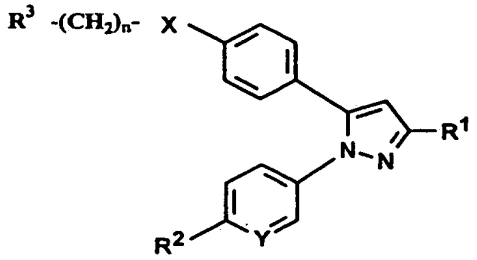
Accordingly, one object of this invention is to provide the azole compounds, which have a COX inhibiting activity.

Another object of this invention is to provide a process for production of the azole compounds.

A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the azole compounds.

Still further object of this invention is to provide a use of the azole compounds for manufacturing a medicament for treating or preventing various diseases.

The new azole compounds of this invention can be represented by the following general formula (I):



(I)

wherein R^1 is lower alkyl which is optionally substituted with

halogen,

cyclo(lower)alkyl,

cyano,

lower alkanoyl,

cyclo(lower)alkylcarbonyl, or
N,N-di(lower)alkylcarbamoyl;

R^2 is lower alkoxy;

R^3 is cyano, or
amino which is optionally substituted with carbamoyl or lower alkanoyl which is optionally substituted with halogen;

X is O;

Y is CH or N; and

n is 1, 2 or 3;

or salts thereof.

The object compound (I) of the present invention can be prepared by processes shown in the Preparations and Examples.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compounds of the formula (I) and its salts can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to

6 carbon atom(s), unless otherwise provided.

Suitable "lower alkyl", and lower alkyl moiety in the term "lower alkoxy" may be a straight or branched one, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl or the like, in which preferable one is methyl or dimethyl.

Suitable lower alkoxy is methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, or the like, in which preferable one is methoxy.

Suitable "halogen" may be fluoro, chloro, bromo or iodo or the like, which preferable one is fluoro.

Suitable "lower alkyl which may be substituted with halogen" may be lower alkyl substituted with one or more halogen atoms(s), such as fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, or the like. And its preferable one is halogen-substituted C1-C2 alkyl. More preferable one is fluorine-substituted methyl, and most preferable one is trifluoromethyl or 2,2,2-trifluoroethyl.

Suitable "cyclo(lower)alkyl" and "cyclo(lower)alkyl moiety" in the term "cyclo(lower)alkylcarbonyl" may include 3 to 8-membered cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like, preferably one having 5 to 7 carbon atoms.

Suitable "N,N-di(lower)alkylcarbamoyl" may be a carbamoyl group substituted with the same or different above lower alkyl groups on nitrogen atom, such as dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, or the like. It is preferably di(C1-C4)carbamoyl, more preferably di(C1-C2 alkyl)carbamoyl.

Suitable "lower alkanoyl" may be formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl,

hexanoyl, or the like.

Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

In order to illustrate the usefulness of the object compounds (I), the pharmacological test data of the compounds (I) are shown in the following.

[A] ANALGESIC ACTIVITY:

Effect on adjuvant arthritis in rats:

(i) Test Method:

Arthritis was induced by injection of 0.5 mg of Mycobacterium tuberculosis (Difco Laboratories, Detroit, Mich.) in 50 μl of liquid paraffin into the right hind footpad of Lewis rats aged 7 weeks. Analgesic activity of a single dose of agents in arthritic rats was studied. Arthritic rats were randomized and grouped (n=10) for drug treatment based on pain threshold of left hind paws and body weight on day 22. Drugs (Test compounds) were administered and the pain threshold was measured 2hr after drug administration. The intensity of hyperalgesia was assessed by the method of Randall - Selitto. The mechanical pain threshold of the left hind paw (uninjected hind paw) was determined by compressing the ankle joint with a balance pressure apparatus (Ugo Basile Co.Ltd., Varese,

Italy). The threshold pressure of rats squeaking or struggling was expressed in grams. The threshold pressure of rats treated with drugs was compared with that of non-treated rats. A dose showing the ratio of 1.5 is considered to be the effective dose.

(ii) Test Results:

Test compound (Example No.)	Dose (mg/kg)	The coefficient of analgesic
3	3.2	>= 1.5
4	3.2	>= 1.5
5	3.2	>= 1.5
12	3.2	>= 1.5
14	3.2	>= 1.5
16	3.2	>= 1.5
17	3.2	>= 1.5

[B] Inhibiting activity against COX-I and COX-II (Whole Blood Assay):

(i) Test Method:

Whole blood assay for COX-I

Fresh blood was collected by syringe without anticoagulants from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection. 500 μl aliquots of human whole blood were immediately incubated with 2 μl of either DMSO vehicle or a test compound at final concentrations for 1hr at 37C to allow the blood to clot. Appropriate treatments (no incubation) were used as blanks. At the end of the incubation, 5 μl of 250mM Indomethacin was added to stop the reaction. The blood was centrifuged at 6000 x g for 5min at 4C to obtain serum. A 100 μl aliquot of serum was mixed with 400 μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4C and was assayed for TXB2 using an enzyme immunoassay kit according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of TXB2 production relative to control incubations containing

DMSO vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC50 value was calculated by least squares method.

Whole blood assay for COX-II

Fresh blood was collected in heparinized tubes by syringe from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection. 500μl aliquots of human whole blood were incubated with either 2μl DMSO vehicle or 2 μl of a test compound at final concentrations for 15min at 37C. This was followed by incubation of the blood with 10μl of 5mg/ml lipopolysaccharide for 24hr at 37C for induction of COX-2. Appropriate PBS treatments (no LPS) were used as blanks. At the end of the incubation, the blood was centrifuged at 6000 x g for 5min at 4C to obtain plasma. A 100μl aliquot of plasma was mixed with 400μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4C and was assayed for PGE2 using a radioimmunoassay kit after conversion of PGE2 to its methyl oximate derivative according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of PGE2 production relative to control incubations containing DMSO vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC50 value was calculated by least squares method.

It appeared, from the above-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against COX, particularly a selective inhibiting activity against COX-I.

(ii) Test Results:

Test Compound (Example No.)	COX-I IC50 (μM)	COX-II IC50 (μM)
3	< 0.01	> 0.1
4	< 0.01	> 0.1
5	< 0.01	> 0.1
12	< 0.01	> 0.1
14	< 0.01	> 0.1
16	< 0.01	> 0.1
17	< 0.01	> 0.1

[C] Inhibiting activity on aggregation of platelet

(i) Methods

Preparation of platelet-rich plasma

Blood from healthy human volunteers was collected into plastic vessels containing 3.8% sodium citrate (1/10 volume). The subject had no taken any compounds for at least seven days prior to blood collection. Platelet-rich plasma was obtained from the supernatant fraction of blood after centrifugation at 1200 r.p.m. for 10 min. Platelet-poor plasma was obtained by centrifugation of the remaining blood at 3000 r.p.m. for 10 min.

Measurement of platelet aggregation

Platelet aggregation was measured according to the turbidimetric method with an aggregometer (Hema Tracer). In the cuvette, platelet-rich plasma was pre-incubated for 2 min at 37C after the addition of compounds or vehicle. In order to quantify the inhibitory effects of each compound, the maximum increase in light transmission was determined from the aggregation curve for 7 min after the addition of agonist. We used collagen as agonist of platelet aggregation in this study. The final concentration of collagen was 0.5µg/mL. The effect of each compound was expressed as percentage inhibition agonist- induced platelet aggregation compared with vehicle treatment. Data are presented as the mean ± S.E.M. for six experiments. The IC_{50} value was obtained by linear

regression, and is expressed as the compound concentration required to produce 50% inhibition of agonist-induced platelet aggregation in comparison to vehicle treatment.

It appeared, from the above-mentioned Test Result, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against platelet aggregation. Therefore, the compound (I) or pharmaceutically acceptable salts thereof are useful for preventing or treating disorders induced by platelet aggregation, such as thrombosis.

Additionally, it was further confirmed that the compounds (I) of the present invention lack undesired side-effects of non-selective NSAIDs, such as gastrointestinal disorders, bleeding, renal toxicity, cardiovascular affection, etc.

The object compound (I) or pharmaceutically acceptable salts thereof of this invention possesses COX inhibiting activity and possesses strong anti-inflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on.

The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing COX mediated diseases, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically.

More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and acute or chronic pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, scapulohumeral periarthritis, cervical syndrome, etc.];
lumbago;
inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.];
inflammatory eye condition [e.g. conjunctivitis, etc.];

lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.]; condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.]; gingivitis; menorrhalgia;
inflammation, pain and tumescence after operation or injury [pain after odontectomy, etc] ;
pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor,
systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, or the like.

Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

The object compound (I) and a salt thereof can be used for prophylactic and therapeutic treatment of arterial thrombosis, arterial sclerosis, ischemic heart diseases [e.g. angina pectoris (e.g. stable angina pectoris, unstable angina pectoris including imminent infarction, etc.), myocardial infarction (e.g. acute myocardial infarction, etc.), coronary thrombosis, etc.], ischemic brain diseases [e.g. cerebral infarction (e.g. acute cerebral thrombosis, etc.), cerebral thrombosis (e.g. cerebral embolism, etc.), transient cerebral ischemia (e.g. transient ischemic attack, etc.), cerebrovascular spasm after cerebral hemorrhage (e.g. cerebrovascular spasm after subarachnoid hemorrhage, etc.), etc.], pulmonary vascular diseases (e.g.

pulmonary thrombosis, pulmonary embolism etc.), peripheral circulatory disorder [e.g. arteriosclerosis obliterans, thromboangiitis obliterans (i.e. Buerger's disease), Raynaud's disease, complication of diabetes mellitus (e.g. diabetic angiopathy, diabetic neuropathy, etc.), phiebothrombosis (e.g. deep vein thrombosis, etc.), etc.], complication of tumors (e.g. compression thrombosis), abortion [e.g. placental thrombosis, etc.], restenosis and reocclusion [e.g. restenosis and/or reocclusion after percutaneous transluminal coronary angioplasty (PTCA), restenosis and reocclusion after the administration of thrombolytic drug (e.g. tissue plasminogen activator (TPA), etc.)], thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation [e.g. surgery (e.g. open heart surgery, pump-oxygenator, etc.) hemodialysis, etc.] or transplantation, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia, essential thrombocytosis, inflammation (e.g. nephritis, etc.), immune diseases, atrophic thrombosis, creeping thrombosis, dilation thrombosis, jumping thrombosis, mural thrombosis, etc.

The object compound (I) and a salt thereof can be used for the adjuvant therapy with thrombolytic drug (e.g. TPA, etc.) or anticoagulant (e.g. heparin, etc.).

And, the compound (I) is also useful for inhibition of thrombosis during extra corporeal circulation such as dialysis.

Particularly, the following diseases are exemplified: pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis, etc; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury; etc.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can

be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting, or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

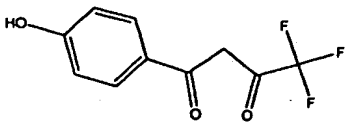
For therapeutic purpose, the analgesic agent of the present invention can be used in a form of pharmaceutical preparation suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like.

Particularly, the analgesic agent of this invention is useful for treating or preventing acute or chronic pains associated with acute or chronic inflammations in human beings or animals by using administered systemically or topically.

The patents, patent applications and publications cited herein are incorporated by reference.

The following Examples are given for the purpose of illustrating the present invention in detail.

Preparation 1



(P1)

To a solution of 4-hydroxybenzophenone (160 g), ethyl trifluoroacetate (182 ml), and ethanol (11 ml) in N,N-dimethylformamide (670 ml) was added portionwise sodium hydride (suspension in mineral oil, 103 g) over 15 minutes at 0 - 35℃. The mixture was stirring at room temperature for 2 hours, and then at 35 - 40℃ for 3 hours.

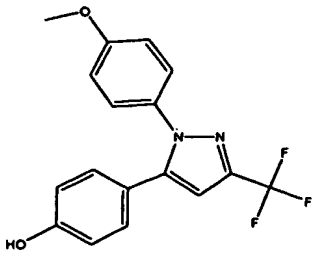
The mixture was poured into a mixture of ice and concentrated hydrogen chloride (320 ml) (aqueous layer total 4L) and diisopropyl ether (2 L). The aqueous layer was separated and extracted with diisopropyl ether (500 ml x 2). The combined organic layers were washed with water (500 ml x 4) and brine, dried over magnesium sulfate, and evaporated to give 415 g of solid.

The solid was dissolved in diisopropyl ether (200 ml) at 65℃. The solution was added dropwise hexane (1.5 L) under stirring at room temperature. After stirring at room temperature for 1 hour, The suspension was filtered and dried under reduced pressure to give solid (first crop, 109.53 g, 40%). The mother liquid evaporated and similarly treated diisopropyl ether (20 ml) and hexane (250 ml) to give second crop (71.11 g, 26%)of P1 (first crop and second crop total, 66.2%).

NMR(CDCl3); 5.65(1H, brs), 6.50(1H, s), 6.94(2H, d, J=8.8 Hz), 7.91(2H, d, J=8.8 Hz).

MS(ESI+), 255.1(M+Na)+.

Preparation 2



(P2)

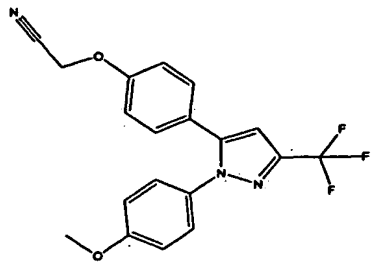
A mixture of P1 (100 g), 4-methoxyphenylhydrazine hydrochloride (82.4 g), and sodium acetate (42.6 g) in acetic acid (550 ml) was stirring at 70℃ for 3 hours. After cooling to room temperature, the mixture was poured into water (4 L) and stirred at room temperature for 1 hour. The precipitate was filtered, washed with water (250 ml x 3) and Hex (500 ml x 2)、and dried at room temperature overnight to give powder (157.86 g)

The powder was purified by recrystallization from ethyl acetate and hexane to give P2 as a powder (121.34g) (77%).

NMR(CDCl3); 3.82(3H, s), 5.08(1H, brs), 6.67(1H, s), 6.77(2H, d, J=8.6 Hz), 6.87(2H, d, J=9.0 Hz), 7.09(2H, d, J=8.6 Hz), 7.23(2H, d, J=9.0 Hz).

MS(ESI+); 357.1(M+Na)+.

Example 1



(E1)

A mixture of P2 (30 g), chloroacetonitrile (8.52 ml), potassium iodide (4.47 g), and potassium carbonate (14.9 g) in acetone (150 ml) was stirring under reflux at 80℃ for 2.5 hours.

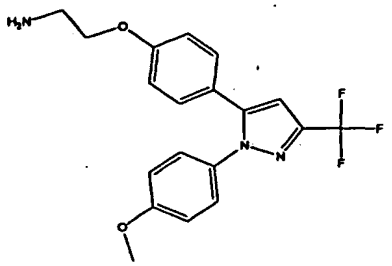
After cooling to room temperature, the mixture was quenched with water (600 ml) and extracted with ethyl acetate (300 ml x 2, 150 ml). The combined organic layers were washed with brine (300 ml), dried over magnesium sulfate, and evaporated to give solid (36.34 g).

The solid was recrysallized from diisopropyl ether (60 ml) and hexane (200 ml) at room temperature to give E1 as a powder (31.5 g, 94%).

NMR(CDCl3), 3.83(3H, s), 4.78(2H, s), 6.70(1H, s), 6.86-6.97(4H, m), 7.18-7.24(4H, m).

IR(KBr), 2051.9cm-1.

Example 2



(E2)

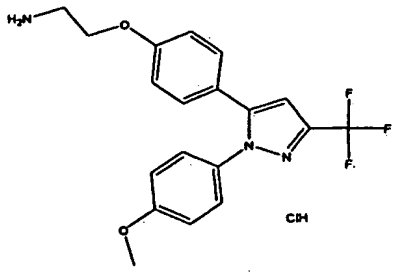
To a suspension of lithium aluminum hydride (250 mg) in ether (14 ml) was added E1 (1.38 g) in ether (5 ml) and tetrahydrofuran (1 ml) under ice-bath. The mixture was stirred at room temperature for 1 hour. Lithium aluminum hydride (50 mg) was added to the mixture under ice-bath., and then the mixture was stirred at room temperature for 1 hour.

The mixture was quenched with water (0.3 ml), sodium hydroxide aqueous solution (15%, 0.3 ml), and water (0.9 ml), and then stirred at room temperature for 30 minutes. Magnesium sulfate and celite was added to the mixture, then the suspension was filtered and washed with ether. The filtrate was evaporated to give 1.307 g of oil. The oil purified with column chromatography (SiO2, 100 ml, eluted with 20% methanol / chloroform (500 ml)) to give E2 as an oil (1.156 g, 82.9%).

NMR(CDCl3), 3.09(2H, t, J=5.1 Hz), 3.82(3H, s), 3.99(2H, t, J=5.1 Hz), 6.67(1H, s), 6.82-6.89(4H, m), 7.14(2H, d, J=8.9 Hz), 7.23(2H, d, J=9.0 Hz).

MS(ESI+), 378(MH+).

Example 3



(E3)

To a solution of E2 (765 mg) in ethyl acetate (1.9 ml) was added a solution of hydrogen chloride in ethyl acetate (4N, 0.56 ml). The mixture was evaporated to give oil, which was crystallized from diisopropyl ether and ethyl acetate at 65℃ to give E3 as a solid (766.8 mg, 91.4%).

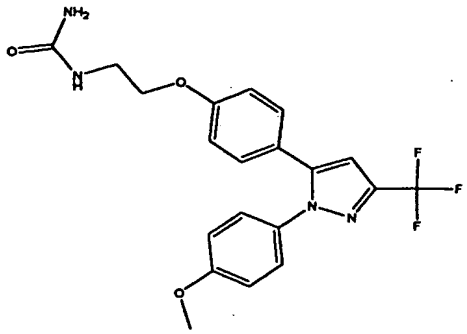
NMR(CDCl3), 3.30(2H, t, J=5.0 Hz), 3.79(3H, s), 4.18(2H, t, J=5.0 Hz), 6.62(1H, s), 6.83-6.88(4H, m), 7.10(2H, d, J=8.8 Hz), 7.18(2H, d, J=8.8 Hz).

NMR(DMSO-d6), 3.19(2H, brs), 3.79(3H, s), 4.18(2H, t, J=5.0 Hz), 6.96-7.01(4H, m), 7.08(1H, s), 7.23-7.29(4H, m).

MS(ESI+), 378.3(MH+, free).

IR(KBr, 20727-2), 1612.2, 1513.9cm-1.

Example 4



(E4)

To a solution of E3 (75.2 mg) in dichloromethane (1 ml) was added triethylamine (30.4 ml) and trimethylsilyl isocyanate (36.9 ml) at 0℃. After stirring for 5 hours, the mixture was quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, and

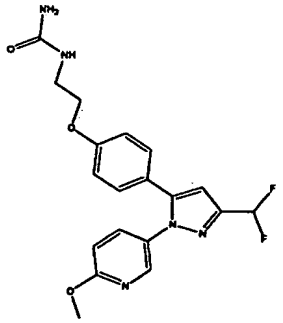
evaporated under reduced pressure to give oil, which was purified with preparative TLC (1 mm, ethyl acetate) to give oil. The oil was crystallized from a mixture of isopropyl ether, ethyl acetate, and hexane to give E4 as a white solid (39.1 mg, 51.2%).

NMR(DMSO-d6); 3.27-3.32(2H, m), 3.79(3H, s), 3.94(2H, t, J=5.6 Hz), 5.52(2H, brs, NH2), 6.15(1H, t, J=5.6 Hz, NH), 6.94(2H, d, J=8.8 Hz), 7.00(2H, d, J=8.9 Hz), 7.07(1H, s), 7.20(2H, d, J=8.8 Hz), 7.28(2H, d, J=8.9 Hz).

MS(ESI+); 443.2(M+Na).

IR(KBr), 1685.5, 1656.6cm-1.

Example 5



(E5)

E5 was prepared in a similar manner to that of E4.

white powder

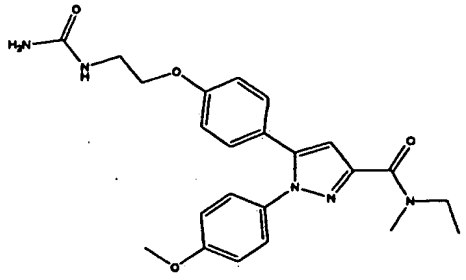
mp. 139-140℃

IR (KBr) : 3458, 3342, 1691, 1647, 1604, 1572, 1529cm-1

Mass (ESI+) : 404 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.28-3.36(2H, m), 3.87(3H, s), 3.92-3.98(2H, m), 5.52(2H, brs), 6.15(1H, t, J=5.5 Hz), 6.88-6.98(4H, m), 7.10(1H, t, J=54.4 Hz), 7.22(2H, d, J=8.7 Hz), 7.69(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz)

Example 6



(E6)

E6 was prepared in a similar manner to that of E4.

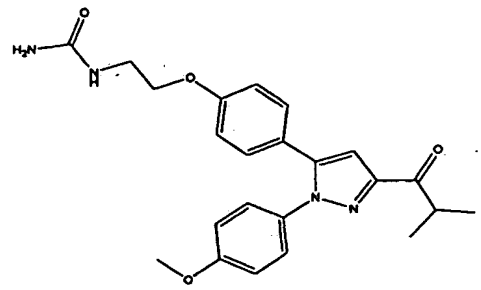
white powdermp. 108-113℃

IR (KBr) : 3492, 3435, 3425, 3359, 3298, 1647, 1614, 1564, 1549, 1512cm-1

Mass (ESI+) : 438 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.08-1.22(3H, m), 2.97,3.29(3H, s), 3.20-3.85(4H, m), 3.78(3H, s), 3.94(2H, t, J=5.5 Hz), 5.53(2H, s), 6.15(1H, t, J=5.6 Hz), 6.79,6.81(1H, s), 6.92(2H, d, J=8.8 Hz), 6.99(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.8 Hz), 7.23(2H, d, J=8.9 Hz)

Example 7



(E7)

E7 was prepared in a similar manner to that of E4.

white powder

mp. 144-145℃

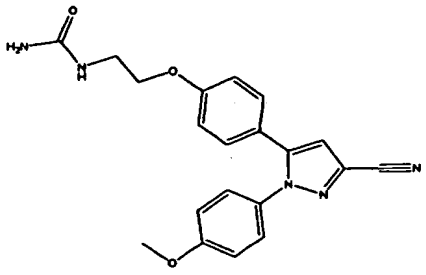
IR (KBr) : 3435, 3369, 3176, 2970, 1674, 1612, 1547, 1514cm-1

Mass (ESI+) : 423 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.15(6H, d, J=6.9 Hz), 3.27-3.36(2H, m), 3.68(1H, m), 3.79(3H, s), 3.90-3.97(2H, m), 5.53(2H, s), 6.15(1H, t, J=5.6 Hz), 6.92(2H, d, J=8.7 Hz), 6.98(1H, s), 7.00(2H,

d, J=8.9 Hz), 7.18(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz)

Example 8



(E8)

E8 was prepared in a similar manner to that of E4.

white powder

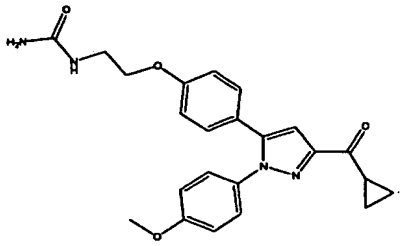
mp. 187-190℃

IR (KBr) : 3379, 3201, 1649, 1614, 1579, 1527, 1506cm-1

Mass (ESI+) : 378 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.27-3.34(2H, m), 3.79(3H, s), 3.94(2H, t, J=5.5 Hz), 5.52(2H, brs), 6.14(1H, t, J=5.6 Hz), 6.94(2H, d, J=8.8 Hz), 7.00(2H, d, J=9.0 Hz), 7.17(2H, d, J=8.8 Hz), 7.24-7.31(3H, m)

Example 9



(E9)

E9 was prepared in a similar manner to that of E4.

white powder

mp. 136-137℃

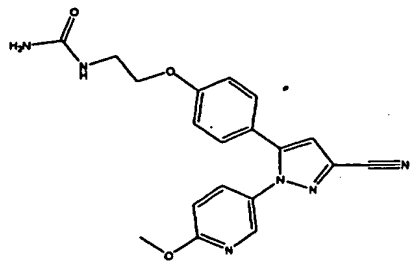
IR (KBr) : 3433, 3342, 3221, 1658, 1612, 1581, 1549, 1512cm-1

Mass (ESI+) : 421 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.04(4H, d, J=6.2 Hz), 3.03(1H, m), 3.27-3.36(2H, m), 3.80(3H, s), 3.90-3.97(2H, m), 5.52(2H, s),

6.14(1H, t, J=5.6 Hz), 6.93(2H, d, J=8.8 Hz), 6.97(1H, s), 7.01(2H, d, J=8.9 Hz), 7.19(2H, d, J=8.8 Hz), 7.30(2H, d, J=8.9 Hz)

Example 10



(E10)

E10 was prepared in a similar manner to that of E4.

white powder

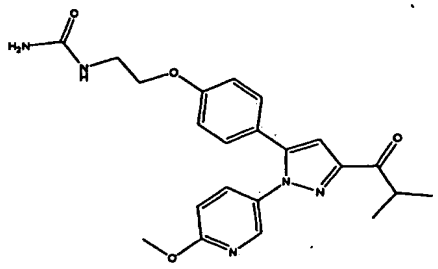
mp. 173-176℃

IR (KBr) : 3473, 3334, 1630, 1624, 1601, 1583cm-1

Mass (ESI+) : 379 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.27-3.36(2H, m), 3.88(3H, s), 3.92-3.98(2H, m), 5.52(2H, s), 6.14(1H, t, J=5.7 Hz), 6.93(1H, d, J=8.8 Hz), 6.97(2H, d, J=8.8 Hz), 7.21(2H, d, J=8.8 Hz), 7.35(1H, s), 7.73(1H, dd, J=2.7,8.8 Hz), 8.20(1H, d, J=2.7 Hz)

Example 11



(E11)

E11 was prepared in a similar manner to that of E4.

white powder

mp. 145-147℃

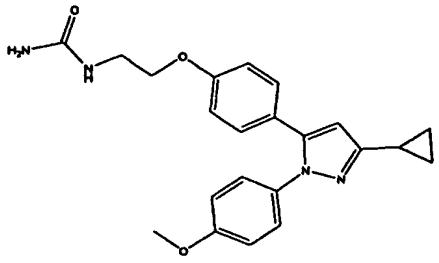
IR (KBr) : 3367, 3174, 2972, 1689, 1674, 1610, 1566, 1502cm-1

Mass (ESI+) : 424 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 3.28-3.37(2H,

m), 3.68(1H, m), 3.88(3H, s), 3.92-3.98(2H, m), 5.52(2H, s), 6.15(1H, t, J=5.6 Hz), 6.93(1H, d, J=8.7 Hz), 6.95(2H, d, J=8.8 Hz), 7.02(1H, s), 7.22(2H, d, J=8.8 Hz), 7.73(1H, dd, J=2.7,8.7 Hz), 8.19(1H, d, J=2.7 Hz)]

Example 12



(E12)

E12 was prepared in a similar manner to that of E4.

white powder

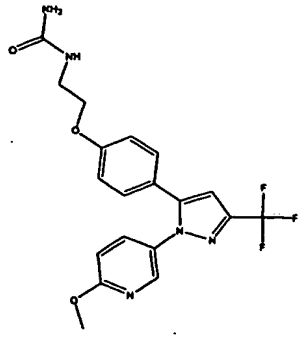
mp. 150.8-151.0℃

IR (KBr) : 3496, 3361, 3294, 1705, 1674, 1647, 1603, 1581, 1568, 1554, 1516cm-1

Mass (ESI+) : 393 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.71-0.77(2H, m), 0.85-0.92(2H, m), 1.92(1H, m), 3.27-3.37(2H, m), 3.76(3H, s), 3.92(2H, t, J=5.5 Hz), 5.51(2H, s), 6.14(1H, t, J=5.5Hz), 6.24(1H, s), 6.86-6.96(4H, m), 7.07-7.15(4H, m)

Example 13

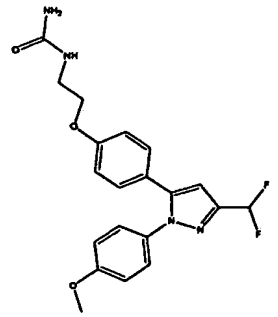


(E13)

E13 was obtained according to a similar manner to that of E4 as an amorphous.

NMR(CDCl3), 3.56-3.64(2H, m), 3.94(3H, s), 4.04(2H, t, J=4.9 Hz), 4.50(2H, brs, NH2), 6.69(1H, s), 6.76(1H, d, J=8.8 Hz), 6.84(2H, d, J=8.8 Hz), 7.12(2H, d, J=8.8 Hz), 7.58(1H, dd, J=8.8, 2.8 Hz), 8.05(1H, d, J=2.8 Hz).
MS(ESI+), 444.1 (M+Na)+. IR(KBr); 1650.8, 1608.3cm-1.
LCMS(ESI+), 422.27(MH+).

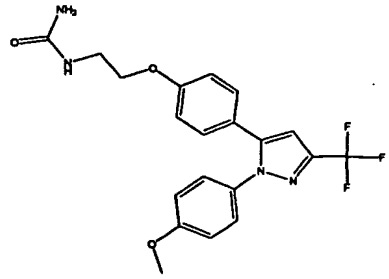
Example 14



(E14)

E14 was obtained according to a similar manner to that of E4 as a powder.
NMR(CDCl3), 3.56-3.64(2H, m), 3.82(3H, s), 4.03(2H, t, J=5.0 Hz), 4.42(2H, brs), 6.65(1H, s), 6.76(1H, t, J=55 Hz), 6.79-6.89(4H, m), 7.14(2H, d, J=8.7 Hz), 7.20(2H, d, J=9.0 Hz).
MS(ESI+), 425(M+Na)+.

Example 15



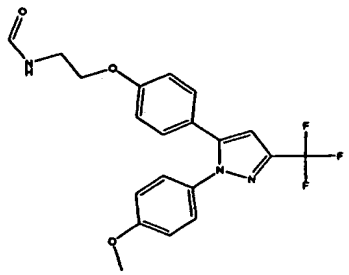
(E15)

To a solution of E3 (15.3 g) in ethanol (75 ml) and hydrogen chloride aqueous solution (1N, 220 ml) was added dropwise a solution of sodium cyanate (14.4 g) in water (300 ml) at 45℃ over 5 minutes. After stirring at 45℃ for 4 hours, the mixture was quenched with

saturated sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated to give powder. The powder was crystallized from ethyl acetate and hexane at room temperature ~70℃ to give E15 as a powder (12.628 g, 81.2%).

The physical data of this compound was identical to E4 obtained in Example 4.

Example 16



(E16)

To a solution of E3 (200 mg) in methanol (1 ml) was added sodium methoxide methanol solution (5.2M, 0.1 ml) at room temperature. After stirring for 20 minutes, the mixture was evaporated to give residue. To the residue was added tetrahydrofuran, and the mixture was filtered and evaporated to give oil.

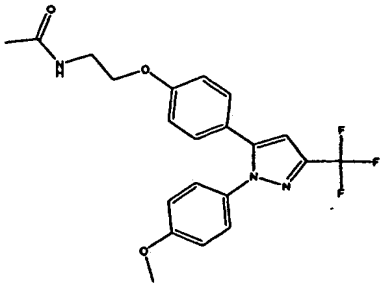
The oil was dissolved in ethyl formate (2 ml) and stirred at room temperature overnight. The mixture was evaporated and purified with preparative TLC(1 mm, 50% ethyl acetate/hexane) to give oil, which was crystallized from isopropyl ether, ethyl acetate, and hexane to give E16 as a white powder (162.8 mg, 83%).

NMR(CDCl3), 3.68-3.76(2H, m), 3.82(3H, s), 4.06(2H, t, J=5.0 Hz), 6.68(1H, s), 6.80-6.89(4H, m), 7.14(2H, d, J=8.7 Hz), 7.22(2H, d, J=9.0 Hz), 8.22(1H, s).

MS(ESI+), 428.2(M+Na).

IR(KBr), 1660.4, 1614.1cm-1.

Example 17



(E18)

To a solution of E3 (800 mg) and triethylamine (0.7 ml) in dichloromethane (9 ml) was added dropwise acetyl chloride (0.18 ml) at 0℃. After stirring at room temperature for 1 hour, the mixture was quenched with saturated sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate (x 3). The combined organic layers were washed with hydrogen chloride aqueous solution (1N), water, and brine, dried over magnesium sulfate, and evaporated to give oil, which was purified with column chromatography (SiO2 100 ml, eluted with 50% ethyl acetate/hexane) to give oil. The oil was crystallized from a mixture of ethyl acetate and hexane at 50℃ to give E17 as a solid (768.6 mg, 94.8%).

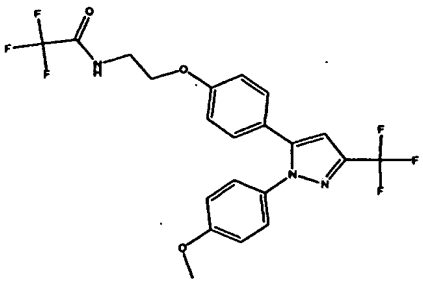
NMR(CDCl3). 2.01(3H, s), 3.62-3.70(2H, m), 3.82(3H, s), 4.03(2H, t, J=5.0 Hz), 6.67(1H, s), 6.80-6.91(4H, m), 7.14(2H, d, J=8.7 Hz), 7.22(2H, d, J=9.0 Hz).

MP; 109.8 - 110.2℃

IR(KBr), 1649cm-1.

MS(ESI+).442.1(M+Na).

Example 18



(E19)

To a solution of E2 (97.5 mg) and pyridine (0.14 ml) in

dichloromethane (1 ml) was added trifluoroacetic anhydride (60.6 ml) at 0℃. After stirring at room temperature overnight, the mixture was quenched with saturated sodium hydrogen carbonate aqueous solution (0.5 ml), filtered with chemelute1001 (Varian), and purified with preparative TLC (1 mm, 50% ethyl acetate/hexane) to give E18 as a solid (92.5 mg, 76%).

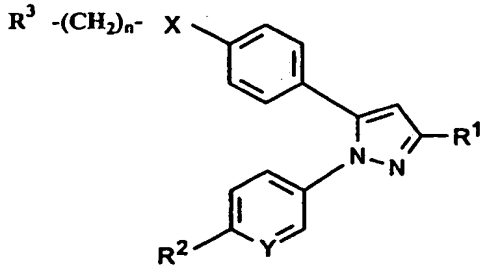
MS(ESI+), 496.1(M+Na).

IR(KBr), 1705cm-1.

NMR(CDCl3),3.75-3.87(2H,m),3.82(3H,s),4.10(4.8H,t),6.68(1H, s), 6.83(2H, d, J=8.8 Hz), 6.88(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.8 Hz), 7.22(2H, d, J=8.9 Hz).

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (I):



(I)

wherein R^1 is lower alkyl which is optionally substituted with
halogen,
cyclo(lower)alkyl,
cyano,
lower alkanoyl,
cyclo(lower)alkylcarbonyl, or
N,N-di(lower)alkylcarbamoyl;
R^2 is lower alkoxy;
R^3 is cyano, or
amino which is optionally substituted with carbamoyl or lower alkanoyl which is optionally substituted with halogen;
X is O;
Y is CH or N; and
n is 1, 2 or 3;
or salts thereof.

2. A pharmaceutical composition comprising the compound (I) or its salts of Claim 1, as an active ingredient, in association with a pharmaceutically non-toxic carrier or excipient.

3. A compound of Claim 1 for use as a medicament

4. A method for treatment and/or prevention of inflammatory

conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases which comprises administering an effective amount of the compound or its salts of Claim 1 to human beings or animals.

5. Use of the compound of Claim 1 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases in human beings or animals.

6. The analgesic agent comprising the compound of Claim 1, which is usable for treating and/or preventing pains caused by or associated with acute or chronic inflammations without causing gastrointestinal disorders.

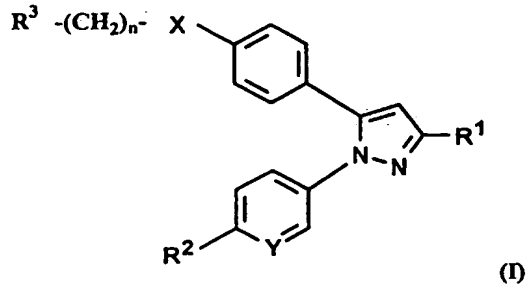
7. The analgesic agent of Claim 6, which is usable for treating or preventing pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, or juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury without causing gastrointestinal disorders.

8. A commercial package comprising the pharmaceutical composition containing the compound (I) identified in Claim 1 and a written matter associated therewith, wherein the written matter states that the compound (I) can or should be used for preventing or treating inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases.

DATED this 2nd day of December 2002
Fujisawa Pharmaceutical Co., Ltd.
By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

A B S T R A C T

A compound of the formula (I):



(I)

wherein R^1 is lower alkyl which is optionally substituted with
halogen,
cyclo(lower)alkyl,
cyano,
lower alkanoyl,
cyclo(lower)alkylcarbonyl, or
N,N-di(lower)alkylcarbamoyl;
R^2 is lower alkoxy;
R^3 is cyano, or
amino which is optionally substituted with carbamoyl
or lower alkanoyl which is optionally substituted
with halogen;
X is O;
Y is CH or N; and
n is 1, 2 or 3;

or salts thereof, which are useful as a medicament.